CADTH

CADTH Drug Implementation Advice

LEVODOPA/CARBIDOPA INTESTINAL GEL (DUODOPA)

Manufacturer: AbbVie Corporation

Indication: For the treatment of patients with advanced levodopa-responsive Parkinson's disease:

- who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of Parkinson's medicinal products, and
- for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) tube required for administration

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Drug	Levodopa/carbidopa intestinal gel (Duodopa)
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Dosage form	Each cassette of 100 mL of gel contains 2,000 mg levodopa and 500 mg carbidopa (monohydrate)
NOC/c date	March 1, 2007
NOC date	March 12, 2014
Manufacturer	AbbVie Corporation

Background

Based on the 2018 review of Duodopa through the CADTH Common Drug Review (CDR), the CADTH Canadian Drug Expert Committee (CDEC) issued the following reimbursement recommendation:

> *The CADTH CDEC recommends that levodopa/carbidopa intestinal gel (LCIG) be reimbursed for the treatment of patients with advanced levodopa-responsive Parkinson's disease (PD) who do not have satisfactory control of motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of PD medicinal products, and for whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the percutaneous endoscopic gastrostomy-jejunostomy tube required for administration, if the following conditions are met:*
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> - *Patients treated with LCIG should be under the care of a neurologist with experience in the treatment of patients with PD who has completed the LCIG education program referenced in the product monograph.*
> - *Reduced price.*

CDEC also recommended that a panel of clinical experts be convened to develop initiation and discontinuation criteria for Duodopa:

> *CDEC noted that appropriately defined initiation and discontinuation criteria for the reimbursement of LCIG are essential to ensure that LCIG is used in patients who are most likely to benefit from it, and to prevent inappropriate use. The Committee recommends that a panel of clinical experts with experience in the treatment of patients with PD be convened to develop initiation and discontinuation criteria for LCIG.*

Consultation Process

CADTH staff contacted several physicians with expertise in the diagnosis and management of patients with PD. The clinical panel consisted of five clinical experts representing four provinces.

One panel meeting was held on December 21, 2018 to discuss appropriate initiation, renewal, and discontinuation criteria for Duodopa. The existing criteria for Duodopa in the Ontario Drug Benefit (ODB) Exceptional Access Program (EAP) were used as a starting point for the panel discussion. In addition to the clinical panellists and CADTH staff, representatives from public drug plans and the pan-Canadian Pharmaceutical Alliance (pCPA) were invited to participate in the discussion as well as provide input in advance of the meeting on topics for discussion.

Following the panel meeting, a draft of the Drug Implementation Advice was prepared by CADTH staff with input from the panellists. CDR-participating drug plans and the manufacturer of Duodopa were given the opportunity to comment on the draft document.

Objectives of the Clinical Panel

The objective of the panel was to reach consensus on appropriate initiation, renewal, and discontinuation criteria for Duodopa that may be used by public drug plans that wish to reimburse Duodopa for patients with advanced levodopa-responsive PD.

Implementation Advice

The panel reached consensus on the following criteria regarding the initiation, renewal, and discontinuation of Duodopa. A summary of the recommended criteria are provided in Table 1. For each criterion, a summary of the relevant panel meeting discussion is provided for context.

Table 1: Summary of Recommended Initiation, Renewal, and Discontinuation Criteria

Initiation Criteria
1. The patient experiences severe disability associated with at least 25% of the waking day in the off state and/or ongoing, bothersome levodopa-induced dyskinesias, despite having tried frequent dosing of levodopa (at least five doses per day). Time in the off state, frequency of motor fluctuations, and severity of associated disability should be assessed by a movement disorder subspecialist and be based on an adequate and reliable account from longitudinal specialist care, clinical interview of a patient and/or care partner, or motor symptom diary. 2. The patient has received an adequate trial of maximally tolerated doses of levodopa, with demonstrated clinical response. 3. The patient has failed adequate trials of each of the following adjunctive medications, if not contraindicated and/or contrary to the clinical judgment of the prescriber: a COMT inhibitor, a dopamine agonist, a MAO-B inhibitor, and amantadine. 4. The patient is able to administer the medication and care for the administration port and infusion pump. Alternatively, trained personnel or a care partner must be available to perform these tasks reliably. 5. The patient does not have a contraindication to the insertion of a PEG-J tube. 6. The patient does not have severe psychosis or dementia.
Renewal Criteria
1. The duration of approval is one year. 2. The patient continues to benefit from treatment. The patient should continue to demonstrate a significant reduction in the time spent in the off state and/or in ongoing, bothersome levodopa-induced dyskinesias, along with an improvement in the related disability.
Discontinuation Criteria
It is expected that physicians will continue to monitor their patients and discontinue Duodopa if the patient is no longer benefiting from treatment, as described for renewal criteria, or if Duodopa is no longer appropriate.
Administration Criteria
Requests for Duodopa initiation will be limited to movement disorder subspecialists who have appropriate training in the use of Duodopa and are practising in movement disorder clinics that provide ongoing management and support for patients receiving treatment with Duodopa.

COMT = catechol-O-methyl transferase; MAO-B = monoamine oxidase-B; PEG-J = percutaneous endoscopic gastrostomy-jejunostomy.

Recommended Initiation Criteria

1. *The patient experiences severe disability associated with at least 25% of the waking day in the off state and/or ongoing, bothersome levodopa-induced dyskinesias, despite having tried frequent dosing of levodopa (at least five doses per day). Time in the off state, frequency of motor fluctuations, and severity of associated disability should be assessed by a movement disorder subspecialist and be based on an adequate and reliable account from longitudinal specialist care, clinical interview of a patient and/or care partner, or motor symptom diary.*

The panellists agreed that patients for whom Duodopa is likely appropriate are those experiencing significant time in the off state and/or disabling levodopa-induced dyskinesias. The panellists considered 25% of the waking day in the off state to be an appropriate threshold for initiating Duodopa. The use of percentage of waking day was preferred over number of hours per day for determining time spent in the off state given variability in the number of hours spent awake. Patients experiencing ongoing frequent levodopa-induced dyskinesias without discrete off times may be suitable candidates for Duodopa. Since time in the off state and severity of motor fluctuations can be increased by reducing the frequency of levodopa administration, patients should be observed in the context of levodopa administration of at least five times a day. Administration of levodopa more than five times a day would be considered an overly burdensome dosage regimen.

Patients being considered for Duodopa should experience severe disability while in the off state or due to ongoing frequent levodopa-induced dyskinesias. The panellists noted that the assessment of the severity of disability should be left to clinical judgment. Degree of disability may depend on the patient's situation; for example, motor fluctuations may have an impact on the function of patients still in their working years differently than in an older, retired patient. Due to the invasiveness of the PEG-J tube placement, the panellists expected that patients would only be willing to undergo the procedure if they were severely affected or disabled by their motor fluctuations.

According to the panellists, the degree of disability and the proportion of the waking day in the off state or with dyskinesia are to be assessed by the subspecialist. This assessment should be based on an adequate and reliable account through longitudinal specialist care, clinical interview of a patient and/or care partner, or motor symptom diary. Care partners may include any personnel involved in the patient's PD care, such as nursing staff in long-term care homes, as long as the information is considered adequate and reliable.

2. *The patient has received an adequate trial of maximally tolerated doses of levodopa, with demonstrated clinical response.*

The panellists did not consider it necessary to define what constitutes an adequate trial of maximally tolerated doses of levodopa or a clinical response, deciding instead to leave these assessments to clinical judgment. As outlined in the first criterion, response to treatment, including that with levodopa can be determined through prolonged clinical observation or reliable accounts of an observer. Motor symptoms in the on and off states can be assessed using a validated scale such as, but not limited to, the motor examination portion of the Unified Parkinson's Disease Rating Scale.

3. *The patient has failed adequate trials of each of the following adjunctive medications, if not contraindicated and/or contrary to the clinical judgment of the prescriber: a catechol-O-methyl transferase (COMT) inhibitor, a dopamine agonist, a monoamine oxidase-B (MAO-B) inhibitor, and amantadine.*

The medications listed above were considered by the panel to be suitable treatment options for patients with advanced PD. However, patients should only be required to try a medication in the absence of any contraindications or other factors that would render its use inappropriate. As an example, the panellists noted that in patients using small doses of levodopa who have a narrow therapeutic range, the introduction of a COMT inhibitor could exacerbate dyskinesias. The panellists preferred to leave the definition of what constitutes an adequate trial of an adjunctive medication up to the physicians' judgment as specifying parameters of an adequate trial would be too restrictive given the potential complexities of trialling these medications. The panellists also preferred to leave to it to physicians' judgment to determine whether a medication failed. The panellists noted that the restriction for only appropriately trained specialists to initiate Duodopa (see Recommended Administration Criteria below) will ensure the physician has the expertise required for such assessments.

The use of apomorphine and deep brain stimulation were also discussed and the panellists did not find a place for them in the initiation criteria for Duodopa. Apomorphine is appropriate for patients with intermittent off times as opposed to frequent motor fluctuations. Deep brain stimulation should be considered independently from other treatments for advanced PD as there are

potential ethical issues related to the risks of the procedure. The panellists also noted that for patients being considered for Duodopa, apomorphine and deep brain stimulation have likely already been ruled out as treatment options based on the aforementioned considerations.

4. *The patient is able to administer the medication and care for the administration port and infusion pump. Alternatively, trained personnel or a care partner must be available to perform these tasks reliably.*

The panellists agreed that the patient must have a care partner or other personnel available to maintain the system if they are not able to do so on their own. Self-administering the morning dose of Duodopa may be especially challenging for a patient in their morning off state.

5. *The patient does not have a contraindication to the insertion of a PEG-J tube.*

It was noted that in most cases a neurologist is able to judge whether a patient is likely to be a suitable candidate for PEG-J tube placement, but that gastroenterologists will frequently be consulted. In terms of logistics, drug plan approval for the use of Duodopa will usually be obtained before the gastroenterology consultation. The panel indicated a gastroenterologist should only be consulted for drug plan approval purposes in cases where the neurologist is uncertain.

6. *The patient does not have severe psychosis or dementia.*

The panel noted that patients with severe psychosis or dementia are excluded under the existing criteria in the ODB EAP as they may not gain meaningful benefit from Duodopa, and patients with severe dementia could pull out their own PEG-J tube due to confusion. There may be some patients with psychosis not well managed on low-to-medium dose neuroleptics whose psychosis is aggravated by motor fluctuations. These patients may benefit from Duodopa if it reduces motor fluctuations and removes the need for constant high doses of anti-PD medications to maintain the on state. The panellists preferred to leave room for clinical judgment on whether psychosis is severe enough to preclude benefit from Duodopa. In patients who have an uncertain likelihood to derive a substantial benefit from Duodopa due to psychosis or dementia, a trial of the drug could be administered through a temporary nasojejunal tube to assess the patient's response and, in the case of patients with dementia, their likelihood of pulling out the tube.

Recommended Renewal Criteria

1. *The duration of approval is one year.*

The panellists agreed that one year was an appropriate interval for the assessment of patients for funding purposes, as specified in the existing ODB EAP criteria. They also agreed that there was no need to specify an earlier time point for assessment following treatment initiation, as Duodopa would be discontinued if the patient was not receiving benefit.

2. *The patient continues to benefit from treatment. The patient should continue to demonstrate a significant reduction in the time spent in the off state and/or in ongoing, bothersome levodopa-induced dyskinesias, along with an improvement in the related disability.*

The panellists were satisfied with the wording for renewal of approval as stated in the existing ODB EAP, but added "ongoing, bothersome levodopa-induced dyskinesias," to mirror the symptoms required for initiation of Duodopa as stated in the first initiation criterion. Rather than further specifying the requirements for demonstrating continued benefit from treatment (i.e., what constitutes "a significant reduction") the panellists considered the current wording to provide the necessary latitude for physicians to assess overall patient benefit. There is heterogeneity expected in the amount of reduction of time spent in the off state and in levodopa-induced dyskinesias that would be needed to effect an improvement in patients' quality of life.

Recommended Discontinuation Criteria

The panellists noted that physicians will continue to monitor their patients for disease progression, appropriateness of the therapy, and/or complications, and discontinue Duodopa if it is no longer appropriate. As mentioned above, Duodopa would be discontinued if the patient was not receiving benefit since the invasiveness and inconvenience associated with the Duodopa system provide a strong disincentive for patients to continue treatment without meaningful benefit.

Recommended Administration Criteria

1. *Requests for Duodopa initiation will be limited to movement disorder subspecialists who have appropriate training in the use of Duodopa and are practising in movement disorder clinics that provide ongoing management and support for patients receiving treatment with Duodopa.*

Most of the aforementioned criteria rely on the clinical judgment of a physician with the appropriate expertise in treating patients with advanced PD and in using Duodopa. Therefore, the panellists emphasized that the prescribing physician must be a movement disorder subspecialist who has appropriate training in the use of Duodopa. It was recognized that some movement disorder subspecialists may not have undertaken a formal fellowship in the subspecialty, but would still have the expertise to be practising within a movement disorder clinic and therefore would qualify.

Duodopa must be initiated at a movement disorder clinic that is able to provide responsive support for patients in case issues arise with the Duodopa system. The panellists did not see the need to restrict the centres eligible for initiating Duodopa beyond the criteria mentioned above. The panellists emphasized that limiting Duodopa treatment to Centres of Excellence (as designated by the National Parkinson Foundation in the US) would add unnecessary and significant barriers to accessing Duodopa.

Additional Guidance

One issue discussed was whether patients should be able to receive two cassettes of Duodopa per day if no longer responsive on one cassette per day. The panellists were against restricting the daily dosage of Duodopa as the dosage needed to control symptoms is specific to each patient. Some patients initiate Duodopa with two cassettes per day. The panellists also noted that the dosage of levodopa is self-limiting in that too much levodopa will cause problematic side effects.

A second issue discussed was the recommendation in the Duodopa product monograph that patients receive Duodopa initially through a temporary nasojejunal tube to test for clinical response. The temporary nasojejunal tube for Duodopa is not routinely used in Canadian clinical practice and would only be considered in patients who may be expected to have an uncertain likelihood to derive a substantial benefit from the drug. As discussed for the sixth initiation criterion, this may include patients with psychosis or dementia.